REMARKS

Entry of the instant amendment and reconsideration of the above-identified application as amended is respectfully requested.

Claims 7, 8, 11-16, 19 and 28-42 are pending in the application.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 7, 8, 11-16, 19 and 28-42 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because claim 7 recites the term "suppressing".

Without conceding the correctness of the rejection, claim 7 has been amended by replacing the term "suppressing" with the term "countering". Support for the amendment may be found throughout the specification, e.g., second full paragraph on page 7, third full paragraph on page 9, and first and second paragraphs on page 13.

In view of the above, it is respectfully submitted that the rejection under 35 U.S.C. § 112, first paragraph, is now moot and should be withdrawn.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 7, 8, 11-16, 19 and 28-42 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,210,917 to Carson et al. in view of U.S. Patent No. 6,066,642 to Jacobson et al. and further in view of Baraldi et al. "Pyrozolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine derivatives as highly potent and selective human A_3 adenosine receptor antagonists", Journal of Medicinal Chemistry *42*, 4473-4478 (1999), and Goodman and Gilman, "The Pharmacological Basis of Therapeutics".

Further to the references above, the Examiner cites Fishman et al., "Adenosine acts as an inhibitor of lymphoma cell growth: a major role for the A_3 adenosine receptor", European Journal of Cancer *36*, 1452-1458 (2000).

A. Carson et al.

Carson et al. teaches a combination therapy comprising an adenosine-5'-triphosphate (ATP) depleting agent to treat cancers such as breast and colon cancer that are multi-

drug resistant (MDR) with respect to vinca alkaloids, taxanes and antibiotics. Carson et al. additionally explains that the depletion of adenosine-5'-monophosphate (AMP) and ATP such that the cells are unable to support P-glycoprotein activity may be employed to treat MDR.

Carson et al. does not teach or suggest, whether taken alone or combined with other references, that adenosine A_3 receptor antagonists could be employed to inhibit P-glycoprotein (P-gp) and multi-drug resistance-associated protein (MRP) mediated drug-efflux (effuse) in cancer cells and, thus, counter MDR, and synergistically enhance the chemotherapeutic treatment of cancer, as disclosed and claimed by the instant invention.

In other words, the method of Carson et al. comprises depriving the cancer cells of the energy required to maintain P-gp mediated drug resistance by employing an ATP depleting agent such as an inhibitor of adenine synthesis (please see, e.g., Abstract; lines 21-28, column 1; and lines 15-26, column 2). To the contrary, the method of the instant invention comprises the use of an adenosine A_3 receptor antagonist to inhibit P-gp and MRP mediated drug-efflux.

As demonstrated by Applicants, adenosine A_3 receptor antagonists of the instant application are direct inhibitors of P-gp mediated drug-efflux in several cancer cell lines and, thus, counter MDR as summarized in the experimental section starting on page 31, last paragraph, and ending on page 34. For example, MRE3008F20 blocks the P-gp mediated rhodamine 123 (Rh 123) transport in A375 cells completely at 10 μM concentration.

In view of the above, and all the limitations set forth in claim 7, it is respectfully submitted that Carson et al., whether taken alone or combined with other references, does not provide one skilled in the art with any motivation, or suggestion, to consider an adenosine A_3 receptor antagonist as an inhibitor of P-gp and MRP mediated drug-efflux and, thus, to attain the instant invention as a whole.

B. Jacobson et al.

Jacobson et al. teaches the use of adenosine A_3 receptor antagonists in the killing of cancer cells (Example 31, column 63), wherein the A_3 receptor antagonists may be used alone, or in combination with other pharmaceutically active compounds.

As to Jacobson et al., it is respectfully submitted that Example 31, although exploring cell death in the presence of adenosine A_3 receptor antagonists, does not show clear evidence whether an adenosine A_3 receptor agonist or an antagonist should be used in the treatment of diseases such as cancers. For example, in accordance with Example 31, last paragraph (column 66), cellular protection as well as programmed cell death can be mediated by both agonists and antagonists, and the level of agonist and antagonist should be carefully balanced to obtain the desired effect on the cells, e.g., death or protection.

However, contrary thereto, a later reference by Fishman et al. discloses convincing evidence showing that the inhibitory effect of adenosine on lymphoma cell growth is abolished in the presence of the adenosine A_3 receptor antagonist MRS-1220 (second full paragraph and Fig. 4 on page 1455), whereas the adenosine A_3 receptor agonist IB-MECA mimicked the inhibitory effect of adenosine (third full paragraph and Fig. 5 on page 1455).

Accordingly, the combined teaching of Jacobson et al. and Fishman et al. suggests that an adenosine A_3 receptor agonist, and not an antagonist, should be employed for the treatment of cancer and, therefore, teaches away from the methods of the instant invention.

C. *Baraldi et al.*

Baraldi et al. teaches that MRE3008F20 is an adenosine A_3 receptor antagonist.

D. *Goodman and Gilman*

Goodman and Gilman teaches that local means of therapy, such as surgery and irradiation, is routinely followed by adjuvant chemotherapy (page 1225). Goodman and Gilman further teaches that drugs are generally more effective in combination and may be synergistic through biochemical interactions (page 1230). Synergy, however, is always unpredictable.

Clearly, none of the references cited herein above, whether taken alone or combined, suggests that adenosine A_3 receptor antagonists could be employed to inhibit P-gp or MRP mediated drug-efflux in tumor cells and, thus, counter MDR, and synergistically enhance the chemotherapeutic treatment of cancer, as is now discovered and demonstrated by the instant invention.

As to the unexpected results, it is the Examiner's opinion that the data set disclosed in the instant application is not convincing. Applicants respectfully disagree:

1) The results shown in Tables 4 to 8, starting on page 23, clearly indicate a synergistic enhancement of the growth inhibitory activity of a number of chemotherapeutic cancer agents in the presence of a sub-cytotoxic concentration of an adenosine A_3 receptor antagonist as determined by the measurement of the enhancement factor greater than 1 (for interpretation of the enhancement factor, please see the paragraph starting on line 29 on page 18). As the results show, synergistic enhancement of the growth inhibitory activity of taxane compounds, e.g., paclitaxel and docetaxel; vinca alkaloids, e.g., vinblastine; camptothecin compounds, e.g., irinotecan; and antibiotics, e.g., doxorubicin; is observed consistently in the presence of an adenosine A_3 receptor antagonist, e.g., MRE3008F20, IL-10 and IL-11, when tested in different cancer cell lines. For example, as illustrated in Example 1 (starting on page 22; Table 4), MRE3008F20 (10 μg/mL), IL10 (5 μg/mL) and IL11 (5 μg/mL) enhanced the growth inhibitory activity of paclitaxel by 8-12 fold against the human melanoma A375 cell line at a sub-cytotoxic concentration, i.e., at a concentration well below the IC_{50} value of each individual antagonist (for individual IC_{50} values, please see Table 3 on page 21).

2) The unexpected synergistic effects of the combination of the present invention are further established, e.g., by colony formation experiments: the adenosine A_3 receptor antagonist MRE3008F20 (10 μM) and the taxane compound paclitaxel (0.75 ng/mL) each alone decreases colony formation of A375 cells to 59 and 64% of the control, respectively. Surprisingly, when MRE3008F20 is combined with paclitaxel, virtually all colony formation ceases. Since the geometrical combination predicts a result of 35%, this clearly identifies the unexpected synergistic nature of combining an adenosine A_3 receptor antagonist with a chemotherapeutic agent (please see second, third and fourth paragraphs on page 27).

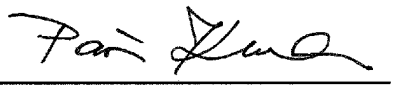
To conclude, it is respectfully submitted that the present invention provides a new therapeutic utility for adenosine A_3 receptor antagonists, i.e., inhibition of P-gp or MRP mediated drug-efflux and, thus, treatment of diseases and disorders associated with P-gp or MRP mediated drug-efflux. Furthermore, the present invention demonstrates, with convincing data, that adenosine A_3 receptor antagonists act synergistically with chemotherapeutic agents, thus, enhancing the chemotherapeutic treatment of cancers.

In view of the foregoing, reconsideration of the rejection of claims 7, 8, 11-16, 19 and 28-32 under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

The instant application is now believed to be in condition for allowance and such is earnestly solicited.

Respectfully submitted,



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